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Alterations in Left Ventricular Function, Coronary Hemodynamics and Myocardial Catecholamine Balance With MDL 17043, a New Inotropic Vasodilator Agent, in Patients With Severe Heart Failure

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To evaluate changes in myocardial energetics and systemic and cardiac sympathetic activity associated with improved left ventricular function after MDL 17043, a new inotropic vasodilator agent, systemic and coronary hemodynamics and myocardial catecholamine balance were determined in 17 patients with severe heart failure. After the administration of MDL 17043, cardiac index increased by 67% and pulmonary capillary wedge pressure decreased (25 ± 5 to 14 ± 7 mm Hg, $p < 0.01$), indicating improved left ventricular function. Coronary sinus blood flow (75 ± 29 to 111 ± 51 ml/min, $p < 0.01$) and myocardial oxygen consumption (9.9 ± 3.3 to 11.8 ± 5.4 ml/min, $p < 0.05$) increased despite decreased myocardial oxygen extraction (11.7 ± 2 to 10.1 ± 3.3 vol %, $p < 0.05$) and a higher coronary sinus oxygen content. Although transmyocardial lactate extraction remained unchanged, increased myocardial oxygen consumption has potential deleterious effects on myocardial metabolic function. Arterial norepinephrine concentrations and transmyocardial norepinephrine release also remained unchanged.

These findings suggest that MDL 17043 improves left ventricular pump function, but produces no detectable change in systemic and cardiac sympathetic activity. Improved left ventricular function is associated with increased myocardial oxygen consumption despite primary coronary vasodilation.

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New pharmacologic agents with both vasodilating and positive inotropic properties have been demonstrated to improve cardiac function in patients with severe heart failure refractory to conventional therapy (1,2). MDL 17043, a nonglycoside, noncatecholamine, imidazole derivative (1,3 dihydro-4-methyl-5-[4-(methylthio)benzoyl]-2H-imidazole-2-one), possesses both positive inotropic and vasodilating effects and improves left ventricular function of patients with severe heart failure (3). However, whether this improvement in left ventricular function is accompanied by a change in cardiac sympathetic tone or myocardial metabolic cost has not been adequately evaluated. The purpose of this study, therefore, was to determine changes in myocardial catecholamine balance, coronary hemodynamics and left ventricular function during MDL 17043 therapy in patients with severe chronic heart failure.

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Methods

Study patients. Seventeen patients formed the study group. There were 12 men and 5 women with a mean age of 57 ± 10 years (range 42 to 69). All patients had clinical evidence of heart failure, radiologic evidence of cardiomegaly and pulmonary venous and arterial hypertension. The cause of heart failure was ischemic cardiomyopathy in 13 patients and dilated congestive cardiomyopathy in the remaining 4 patients. At the time of investigation, 14 patients were in New York Heart Association functional class IV and 3 were in class III. Eleven patients had a prior myocardial infarction and six gave a history of hypertension; however, no patient had hypertension at the time of the study. Fourteen patients were taking digitalis and 16 were on diuretic therapy. Vasodilators, including nitrates, were discontinued at least 24 hours before study.

Hemodynamic and metabolic studies. Patients were studied in the resting, nonsedated state in the cardiac care

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unit of Moffitt Hospital at the University of California, San Francisco. Written informed consent was obtained from all patients. A triple lumen thermistor Swan-Ganz catheter was positioned in the pulmonary artery percutaneously through the subclavian vein, to measure cardiac output and right atrial, pumonary arterial and pulmonary capillary wedge pressures (4). Cardiac output was determined by the thermodilution technique. The radial artery was cannulated for direct measurement of the arterial pressure. Under fluoroscopic guidance, a double thermistor catheter (Wilton-Webster Laboratories) was placed percutaneously in the coronary sinus. To minimize coronary sinus reflux, the catheter was advanced into the midcoronary sinus and its position checked by a small bolus injection of contrast medium (5).

Coronary sinus flow was determined by constant infusion thermodilution (6) using the formula:

$$\text{Coronary sinus flow (ml/min)} = \left(\frac{T_B - T_I}{T_B - T_M} - 1\right) \times 1.08 \times 46,$$

where T_B = temperature of the blood; T_I = temperature of the indicator; T_M = temperature of the mixture of the blood and indicator; 1.08 = a constant accounting for specific heat and density of blood and the indicator; 46 = the injection rate (ml/min) of the indicator (5% dextrose in water) through a Harvard constant infusion pump. We previously reported (7) the reproducibility of measurements of coronary sinus flow. When estimated by computing the difference in mean values (± standard deviation) of those measurements where the baseline heart rate-systolic blood pressure product varied no more than 10%, the difference in coronary sinus flow was 0.1 ± 4.02 ml/min.

After a rest period of at least 30 minutes following the positioning of the catheters, blood was drawn simultaneously from the coronary sinus and the radial artery for determination of catecholamine concentrations, oxygen saturation and lactate concentration. Systemic hemodynamics, cardiac output and coronary sinus flow were then determined.

Plasma epinephrine and norepinephrine were measured with the radioenzymatic technique using a modified method of Peuler and Johnson (8). Replicate measurements in our laboratory of plasma epinephrine and norepinephrine have a coefficient of variation of 7 and 11%, respectively. Normal laboratory values in supine subjects are as follows: epinephrine, 35 to 165 pg/ml; norepinephrine, 100 to 550 pg/ml (both +3 standard deviations).

The lactate concentration was measured by the enzymatic fluorometric method of Loomis (9) and oxygen saturation was measured with a Corning 175 automated blood and pH analyzer.

Calculations. *The hemodynamic and metabolic variables were calculated as follows:*

Oxygen content (vol %) = Oxygen saturation × Hemoglobin × 1.34.

Myocardial oxygen extraction (vol %) = Arterial oxygen content − Coronary sinus oxygen content.

Myocardial oxygen consumption (ml/min) = Arterial oxygen content − Coronary sinus oxygen content × Coronary sinus flow × 10^{-2}.

Myocardial oxygen delivery (ml/min) = Arterial oxygen content × Coronary sinus flow × 10^{-2}.

Myocardial lactate extraction (%) = $\left(\frac{\text{Arterial} - \text{Coronary sinus}}{\text{Arterial}}\right)$ lactate × 100.

Cardiac index (liters/min per m²) = Cardiac output/Body surface area.

Stroke volume index (ml/m²) = Cardiac index/Heart rate.

Stroke work index (g-m/m²) = (Mean systolic arterial pressure − Mean pulmonary capillary wedge pressure) × Stroke volume index × 0.0136.

Systemic vascular resistance (dynes·s·cm^{-5}) = [(Mean arterial pressure − Mean right atrial pressure)/Cardiac output] × 80.

Pulmonary vascular resistance (dynes·s·cm^{-5}) = [(Mean pulmonary artery pressure − Mean right atrial pressure)/Cardiac output] × 80.

Net transmyocardial epinephrine release (pg/min) = (Arterial − Coronary sinus) epinephrine × Coronary sinus flow.

Net transmyocardial norepinephrine release (pg/min) = (Arterial − Coronary sinus) norepinephrine × Coronary sinus flow.

MDL 17043 administration and repeat measurements. After the control measurements, MDL 17043 was administered by slow intravenous infusion every 15 minutes in doses of 0.5, 1.0 and 1.5 mg/kg. Hemodynamic variables were measured immediately after each dose and at approximately 10 minutes after each dose. Subsequent doses of 1.5 mg/kg were administered at 15 minute intervals until cardiac output response stabilized, heart rate increased by more than 15% or to 120 beats/min, systolic blood pressure decreased by more than 20% or below 85 mm Hg, pulmonary capillary wedge pressure decreased to less than 10 mm Hg or a cumulative dose of 10 mg/kg was administered. Peak effect was defined when the maximal increase in cardiac output was achieved and after which no further significant increment occurred on the basis of the degree of variability in determination of cardiac output in the group (67% confidence limits).

At the time when there was no further increase in cardiac output, coronary sinus, venous and arterial blood samples were drawn simultaneously for repeat measurements of catecholamine concentrations, oxygen saturation and lactate concentration. Systemic hemodynamics and coronary sinus flow were then determined.

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Table 1. Changes in Systemic Hemodynamic Effects in 17 Patients With Severe Heart Failure After MDL 17043

	Baseline	Peak	p Value
Heart rate (beats/min)	84 ± 12	93 ± 15	<0.01
Mean blood pressure (mm Hg)	78 ± 11	70 ± 7	<0.01
Mean right atrial pressure (mm Hg)	13 ± 8	8 ± 7	<0.01
Mean pulmonary artery pressure (mm Hg)	38 ± 7	28 ± 8	<0.01
Pulmonary capillary wedge pressure (mm Hg)	25 ± 5	14 ± 7	<0.01
Cardiac index (liters/min per m^2)	2.1 ± 0.7	3.5 ± 0.9	<0.01
Stroke volume index (ml/m^2)	26 ± 9	38 ± 9	<0.01
Pulmonary vascular resistance (dynes·s·cm^{-5})	284 ± 143	207 ± 103	<0.05
Systemic vascular resistance (dynes·s·cm^{-5})	1,450 ± 567	868 ± 296	<0.01
Stroke work index (g-m/beats per m^2)	27 ± 14	41 ± 14	<0.01

Data are reported as mean ± standard deviation.

Statistics. The paired t test was used to determine the statistical significance of the difference in variables at baseline and at peak effect. The confidence intervals for the measured differences were calculated as follows (10):

$$\text{Difference} = \text{Measured difference} \pm t_{\alpha/2}\frac{s}{\sqrt{n}},$$

where $\alpha = 0.05$ to produce 95% confidence intervals; $t_{\alpha/2}$ = t value for $n-1$ degrees of freedom; s = standard deviation of the differences and n = number of pairs.

Results

Changes in systemic hemodynamics. The systemic hemodynamic effects of intravenous MDL 17043 in all 17 patients are summarized in Table 1. The mean cumulative dose of MDL 17043 administered was 3.6 mg/kg (range 0.5 to 10). The mean time to peak drug effect was 27 minutes.

After the administration of MDL 17043, there was a statistically significant increase in heart rate and a decrease in mean arterial pressure; however, these changes were small. There was a marked decrease in right atrial, pulmonary arterial and pulmonary capillary wedge pressures and in pulmonary and systemic vascular resistance. Cardiac index (+67%), stroke volume index (+46%) and stroke work index (+52%) increased in all patients along with a decrease in pulmonary capillary wedge pressure, indicating improved left ventricular pump performance.

Changes in coronary hemodynamics. The changes in coronary hemodynamics and myocardial metabolic function are summarized in Table 2. In 12 of 16 patients, coronary sinus blood flow increased (Fig. 1), and in the group as a whole, this increase was significant ($p < 0.01$). Heart rate-systolic blood pressure product tended to be higher after MDL 17043, although these changes were not statistically significant. Myocardial oxygen extraction, determined in 16 of 17 patients, tended to decrease, partly because of a slight but statistically significant decrease in arterial oxygen content (Fig. 2). However, in 11 of 16 patients, coronary sinus oxygen content was higher (Fig. 3). Calculated myocardial oxygen delivery increased significantly and, despite a lower myocardial oxygen extraction, myocardial oxygen consumption increased. Transmyocardial lactate extraction was unchanged. Myocardial lactate production did not occur in any patient after the administration of MDL 17043. In one patient, lactate production was observed both before and after MDL 17043.

Myocardial catecholamine balance. The changes in arterial and coronary sinus venous catecholamine concentation and myocardial catecholamine balance after MDL 17043 administration are summarized in Table 3. Coronary sinus

Table 2. Changes in Coronary Hemodynamics in 17 Patients With Severe Heart Failure After MDL 17043

	Baseline	Peak	p Value
Myocardial oxygen extraction (vol %)	11.7 ± 2.0	10.1 ± 3.3	<0.05
Myocardial oxygen delivery (ml/min)	12.0 ± 4.3	16.4 ± 9.6	<0.05
Myocardial oxygen consumption (ml/min)	8.9 ± 3.3	11.8 ± 5.4	<0.05
Lactate extraction (%)	27 ± 19	21 ± 19	NS
Coronary sinus flow (ml/min)	75 ± 29	111 ± 51	<0.01
HR × SBP × 10^{-3} (mm Hg/min)	8.9 ± 1.5	10.4 ± 1.9	NS

Data are reported as mean ± standard deviation. HR = heart rate; NS = not significant; SBP = systolic blood pressure.

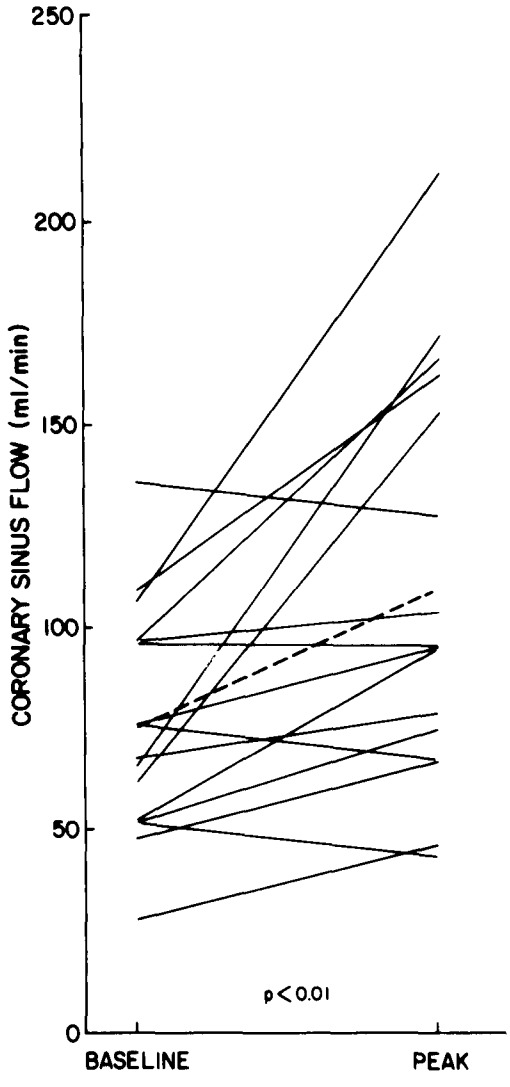

Figure 1. Changes in coronary sinus blood flow (ml/min) after MDL 17043 in 16 patients with severe heart failure. In 12 of the 16 patients, coronary sinus blood flow increased and left ventricular function improved. The **dashed line** indicates the average increase in coronary sinus blood flow from 75 ± 29 to 111 ± 51 ml/min.

venous epinephrine concentrations were lower than arterial epinephrine concentrations both before and after MDL 17043, and myocardial epinephrine balance (uptake) was unchanged. Coronary sinus venous norepinephrine concentrations, however, were higher than arterial norepinephrine values. There was no statistically significant change in net myocardial norepinephrine release (change of 1.41×10^4 pg/min with 15% confidence limits of $+0.99 \times 10^4$ to -3.8×10^4 pg/min). Arterial norepinephrine concentrations were higher than those found in subjects without heart failure, but there was no statistically significant change after MDL 17043 (change of −59 pg/ml with 95% confidence limits of +194 to −312 pg/ml).

Discussion

Systemic hemodynamics. This study confirms that MDL 17043 administered intravenously produces marked improvement in left ventricular function in patients with severe chronic congestive heart failure (3). Enhanced left ventricular pump function was evident from the concomitant increase in cardiac index, stroke volume and stroke work indexes and marked decrease in pulmonary capillary wedge pressure. This study, however, does not elucidate the potential mechanisms for improved left ventricular function with MDL 17043, except that the reduction of left ventricular outflow resistance must have been contributory since there was a marked reduction in systemic vascular resistance and some decrease in arterial pressure.

Coronary hemodynamics. This study also suggests that improved left ventricular function is associated with increased myocardial oxygen consumption. Coronary sinus blood flow and total myocardial oxygen delivery increased in our patients after the administration of MDL 17043. The increase in coronary sinus flow determined by thermodilution technique cannot be explained by the changes in coronary sinus reflux (5) because after MDL 17043, there was a significant reduction in right atrial pressure which should be associated with decreased coronary sinus reflux. Thus, the increase in coronary sinus flow after the administration of MDL 17043 in these patients was probably underestimated.

Increased myocardial oxygen requirements and increased cardiac blood flow. A decreased myocardial oxygen extraction after MDL 17043 was partly caused by decreased arterial oxygen content, presumably due to a marked increase in cardiac output and transpulmonary shunt. However, the decrease in myocardial oxygen extraction was primarily due to the increased coronary sinus venous oxygen content. The reduction in myocardial oxygen extraction and a higher coronary sinus venous oxygen content, in most of our patients, raises the possibility that the drug-induced primary decrease in coronary vascular resistance is a possible mechanism for increased coronary blood flow. Where the increment in coronary blood flow occurs entirely because of an increased myocardial oxygen requirement, the global myocardial oxygen extraction either remains unchanged or increases; the coronary sinus venous oxygen content also remains unchanged or decreases. Thus, a decreased myocardial oxygen extraction and a higher coronary sinus venous oxygen content strongly suggest primary coronary vasodilation by MDL 17043. Because myocardial oxygen consumption also increased, however, the increase in coronary blood flow also must have resulted from the concomitant increase in myocardial oxygen requirements.

The mechanism for the increased myocardial oxygen demand in these patients after MDL 17043 administration remains unclear. Peak systolic arterial pressure or heart rate-

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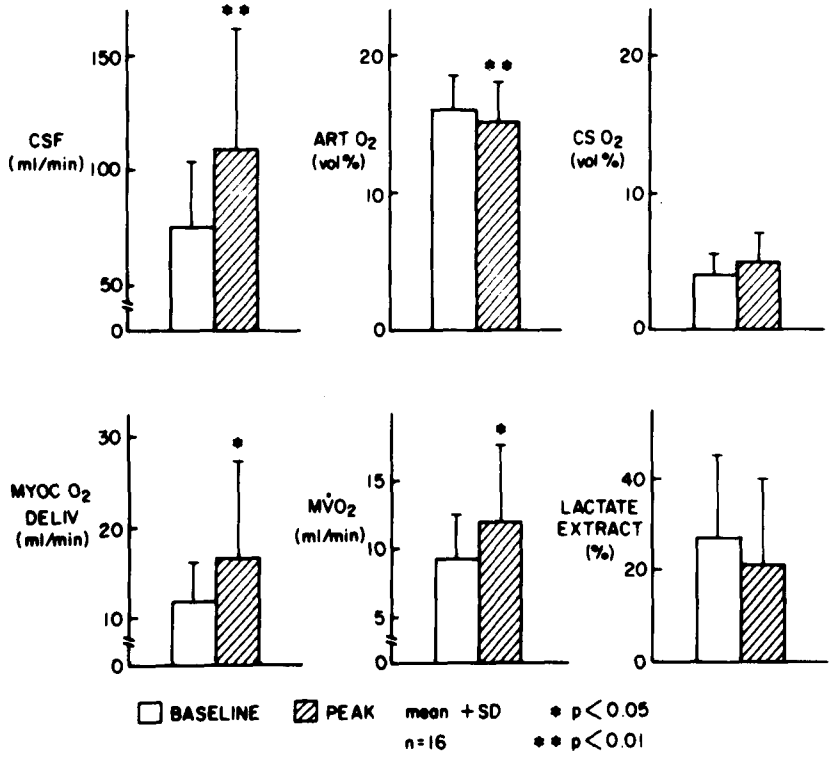

Figure 2. Average changes in coronary sinus flow (CSF), arterial oxygen content (ART O_2), coronary sinus oxygen content (CS O_2), myocardial oxygen delivery (MYOC O_2 DELIV), myocardial oxygen consumption ($M\dot{V}O_2$) and lactate extraction (LACTATE EXTRACT) after MDL 17043 in 16 patients with severe heart failure. Myocardial oxygen consumption increased despite decreased arterial oxygen content and a higher coronary sinus oxygen content, suggesting that increased coronary sinus blood flow and myocardial oxygen delivery after MDL 17043 were primarily related to increased myocardial oxygen demand.

blood pressure product did not change significantly. However, there was a tendency to higher rate-pressure product, which might have contributed to increased myocardial oxygen requirements. The changes in contractile function were not evaluated in this study.

Ventricular function. In patients with heart failure, the first derivative of left ventricular pressure (dP/dt) increases despite a lower arterial pressure and unchanged heart rate, suggesting increased contractility (11). It appears, therefore, that MDL 17043 has the potential to increase contractile function, which might be contributory to increased myocardial oxygen demand and consumption in patients with heart failure.

In preliminary studies (12), it has been suggested that apparent left ventricular diastolic compliance may increase in some patients. We observed that in approximately 50% of patients with chronic heart failure, radioangiographically determined left ventricular volume increased after MDL 17043 despite a marked decrease in pulmonary capillary wedge pressure. Although the mechanisms for such changes have not been elucidated, an increase in left ventricular diastolic volume with little or no decrease in arterial pressure is likely to increase left ventricular wall tension and, thus, myocardial oxygen demand and consumption in some patients. Further studies, however, will be required to determine the relative contributions of the changes in the different determinants of myocardial oxygen demand in increasing myocardial oxygen consumption after MDL 17043.

Myocardial lactate extraction and myocardial ischemia. In our patients, transmyocardial lactate extraction remained unchanged despite increased myocardial oxygen consumption, indicating the lack of biochemical evidence for myocardial ischemia after MDL 17043. However, in a preliminary study, Martin et al. (13) reported that in some patients myocardial lactate production occurred after intravenous MDL 17043. These investigators also observed increased coronary sinus blood flow and myocardial oxygen consumption and decreased myocardial oxygen extraction (results that were similar to those in our study). Martin et al. suggested that myocardial lactate production in some of their patients was due to intercoronary shunts since there was a decrease in myocardial oxygen extraction in the presence of increased myocardial oxygen consumption. However, an inadequate increase in coronary blood flow in relation to the increase in myocardial oxygen demand in the relatively ischemic zone and an increase in flow in excess of metabolic demand in the nonischemic zones can also explain myocardial ischemia despite decreased global myocardial oxygen extraction. It needs to be emphasized that regional myocardial ischemia may not be detected when one examines changes in global lactate extraction, as was done in this and previous studies.

Myocardial catecholamine balance. That enhanced systemic and cardiac sympathetic tone accompany heart failure associated with low cardiac output has been documented (14–16). Arterial norepinephrine concentrations reflect sys-

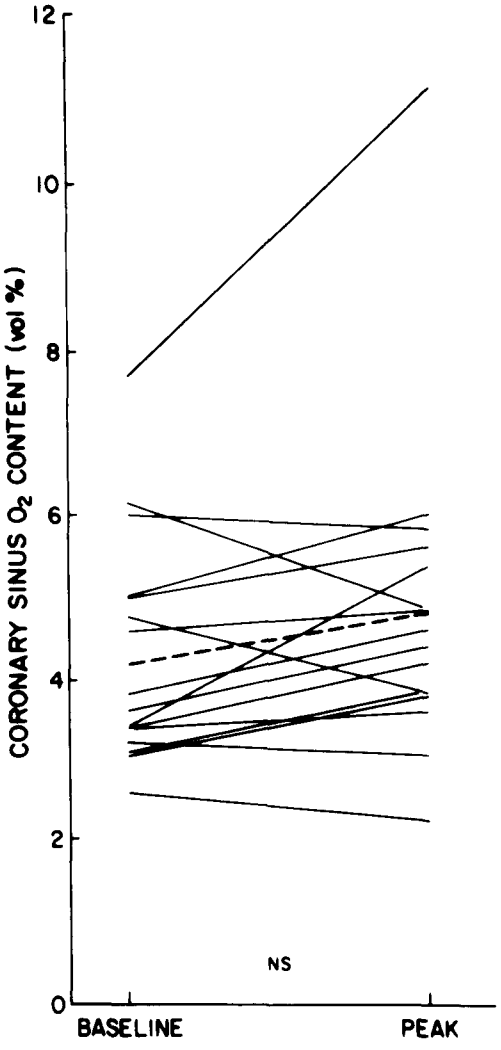

Figure 3. Changes in the coronary sinus oxygen content after MDL 17043 in 16 patients with severe heart failure. In 11 of the 16 patients, coronary sinus oxygen content increased, suggesting primary coronary vasodilation by MDL 17043. NS = not significant.

temic sympathetic activity, whereas changes in net myocardial norepinephrine release can be used to assess cardiac sympathetic activity. In our patients, arterial norepinephrine concentration before MDL 17043 was higher than that expected in patients without heart failure (16). Net myocardial norepinephrine release was also greater than what has been reported in patients without heart failure. Thus, there was evidence for heightened systemic and cardiac sympathetic activity in our patients before MDL 17043. After the administration of MDL 17043, there was no change either in arterial norepinephrine concentration or in net myocardial norepinephrine release despite marked improvement in left ventricular function. Increased sympathetic activity has been regarded as a reflex response to depressed left ventricular function in patients with heart failure. Thus, improved left ventricular function with MDL 17043 was expected to decrease sympathetic activity in our patients. However, despite the marked increase in cardiac output and virtually no change in arterial pressure, arterial norepinephrine concentration and net myocardial norepinephrine release remained unchanged after MDL 17043.

These findings suggest that immediate improvement in left ventricular function with MDL 17043 is not associated with reflex decrease in systemic or cardiac sympathetic activity. However, this is a short-term study and it remains to be determined whether there is a statistically significant change in catecholamine balance after a long-term improvement in ventricular function. Also, the failure to detect a significant change must be interpreted with caution. Power analysis based on 95% confidence intervals shows that we cannot exclude a decrease from baseline of less than 300 pg/ml for arterial norepinephrine and of less than 2.4×10^4 pg/min for net transmyocardial norepinephrine release. Whether these magnitudes of decrease are clinically significant remains to be determined. This insensitivity for detecting a decrease is due to a high standard deviation among the base to peak differences.

Table 3. Changes in Circulating Catecholamines and Myocardial Catecholamine Balance in 17 Patients With Severe Heart Failure After MDL 17043

	Baseline	Peak	p Value
ART epinephrine (pg/ml)	113 ± 155	70 ± 87	NS
CS epinephrine (pg/ml)	90 ± 141	61 ± 82	NS
TmR epinephrine (pg/min)	$-1.92 \times 10^3 \pm 2.33 \times 10^3$	$-1.00 \times 10^3 \pm 4.53 \times 10^3$	NS
ART norepinephrine (pg/ml)	846 ± 744	787 ± 526	NS
CS norepinephrine (pg/ml)	1,461 ± 1,301	1,131 ± 996	NS
TmR norepinephrine (pg/ml)	$5.17 \times 10^4 \pm 5.44 \times 10^4$	$3.13 \times 10^4 \pm 6.78 \times 10^4$	NS

Data are reported as mean ± standard deviation. ART = arterial; CS = coronary sinus; NS = not significant; TmR = transmyocardial release.

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Conclusion. The results of the present investigation suggest that MDL 17043 improves left ventricular function in patients with severe refractory heart failure. Improved left ventricular function, however, is associated with increased myocardial oxygen consumption, which might have potential deleterious effects on myocardial metabolic function. Coronary vasodilation may also occur since there was decreased oxygen extraction and higher coronary sinus venous oxygen content in many patients after MDL 17043. Despite improved left ventricular function with MDL 17043, systemic and cardiac sympathetic activity remains unchanged.

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